1615
2.4/declaration

PATENT APPLICATION 1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

NISHIBE, Yoshihisa, et al.

Docket No: Q71074

Divisional of Appln. No.: 09/446,276

Group Art Unit: Not Yet Assigned

Confirmation No.: Unknown

Examiner: Not Yet Assigned

Filed: July 24, 2002

For: PHARMACEUTICAL COMPOSITION FOR APPLICATION TO MUCOSA

SUBMISSION OF EXECUTED DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
Washington, D.C. 20231

Sir:

Submitted herewith, as a Supplemental to the Preliminary Amendment filed on July 24, 2002, is an executed Declaration Under 37 C.F.R. § 1.132 signed by Atsuhiro Nagano.

The Declaration shows unexpectedly superior results of the claimed invention in that an osmotic pressure of "285 mOsm", which is just below the upper limit of "less than 290 mOsm", unexpectedly provides better bioavailability than the osmotic pressure of "290 mOsm" just above the upper limit of "less than 290 mOsm", with a statistically significant difference.

Respectfully submitted,

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Date: August 8, 2002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Yoshihisa NISHIBE, et al.
Serial No.: 09/446,276
Filed: December 21, 1999
For: MEDICINAL COMPOSITIONS FOR APPLICATION TO MUCOSA

Group Art Unit : 1615
Examiner : Amy E Pulliam

DECLARATION UNDER 37 C.F. 1.132

Hon. Commissioner of Patents and Trademarks,
Washington, D.C. 20231

Sir:

I, Atsuhiro Nagano, c/o TEIJIN LIMITED, Pharmaceutical Products Research Laboratories, 4-3-2 Asahigaoka, Hino, Tokyo191-8512, Japan, do hereby declare:

That I am by profession a research scientist having earned a Master's degree in technology from Kyoto University in March 1998;

That I have been employed by TEIJIN LIMITED, Tokyo, Japan, since March 1998;

That I have been engaged in research into the development of pharmaceutical products in the same company to date;

That I am fully familiar with the above-identified U.S. application (hereinafter referred to as "present invention" for brevity);

That I have read and am fully familiar with the art cited against claims of the above-identified U.S. application (hereinafter referred to as "present application" for brevity);

That I personally conducted or supervised the conduct of all of the work reported in the examples including the comparative example in the specification of the present application, and the results obtained are as set forth therein;

That , to show that the present invention should be patentable, I carried out the following explanations.

I would like to explain that the criticality of the osmolarity of the present invention. Namely compositions which have osmolarity of less than 290 mOsm have an effect of the present invention, but compositions which have osmolarity of 290 mOsm or more do not have the effect.

1. Preparation

Following compositions (No. A to D) were prepared.

Composition A : Osmolarity 290 mOsm
- Fluorescein : 0.1%(w/w)
- Crystalline cellulose carmellose sodium : 1.7%(w/w)
- Polysorbate 80 : 0.1%(w/w)
- Benzalkonium chloride : 0.03%(w/w)
- Glucose : 4.7%(w/w)

Composition B : Osmolarity 285 mOsm
- Fluorescein : 0.1%(w/w)
- Crystalline cellulose carmellose sodium : 1.7%(w/w)
- Polysorbate 80 : 0.1%(w/w)
- Benzalkonium chloride : 0.03%(w/w)
- Glucose : 4.5%(w/w)

Composition C : Osmolarity 250 mOsm
- Fluorescein : 0.1%(w/w)
- Crystalline cellulose carmellose sodium : 1.7%(w/w)
- Polysorbate 80 : 0.1%(w/w)
- Benzalkonium chloride : 0.03%(w/w)
- Glucose : 4.0%(w/w)

Composition D : Osmolarity 90 mOsm
- Fluorescein : 0.1%(w/w)
- Crystalline cellulose carmellose sodium : 1.7%(w/w)
- Polysorbate 80 : 0.1%(w/w)
- Benzalkonium chloride : 0.03%(w/w)
- Glucose : 1.5%(w/w)

2. Absorption test

Compositions A to D abovementioned and compositions 12 and 7 of the present invention were intranasally administered to rabbits and then, plasma fluorescein concentration of each composition was determined by HPLC, according to the description in the present specification (see lines 6-17, page 13).

Compositions 12 and 7 of the present invention (see Table 2, page 16 and Table 1, page 14) are as follows.

Composition 12 : Osmolarity 340 mOsm
- Fluorescein : 0.1%(w/w)
- Crystalline cellulose carmellose sodium : 1.7%(w/w)
- Polysorbate 80 : 0.1%(w/w)
- Benzalkonium chloride : 0.03%(w/w)
- Glucose : 5.0%(w/w)

Composition 7 : Osmolarity 128 mOsm
- Fluorescein : 0.1%(w/w)
- Crystalline cellulose carmellose sodium : 1.7%(w/w)
- Polysorbate 80 : 0.1%(w/w)
- Benzalkonium chloride : 0.03%(w/w)
- Glucose : 2.1%(w/w)

Furthermore, the significance of plasma fluorescein concentration, between composition A (290mOsm) and compositions 7 and B-D (less than 290mOsm), and between composition A (290mOsm) and composition 12(340mOsm), were statistically analyzed. The statistical analysis was the t-test that is used generally in the field of bioscience. The result was shown in Table 1 and Graph 1.

The effectiveness of this invention was evaluated by the plasma concentration of the fluorescein that is a model drug. The reason why we evaluated the plasma fluorescein concentration as an indicator is as follows.

Pharmaceutical compositions for application to mucosa were expected to make systemic action or topical action.

In the case of systemic drug, intranasally administered drug penetrates to mucus tissue and then reaches the blood circulation. The drug in the blood circulation is distributed to the target site. So, plasma drug concentration can be an indicator that evaluates the effectiveness for systemic drug.

In the case of topical drug, intranasally administered drug penetrates to mucus tissue and works there. Some proportion of the drug in the mucus tissue reaches the blood circulation by the gradient of drug concentration. So, plasma drug concentration can be also the indicator that evaluates the effectiveness for local drug.

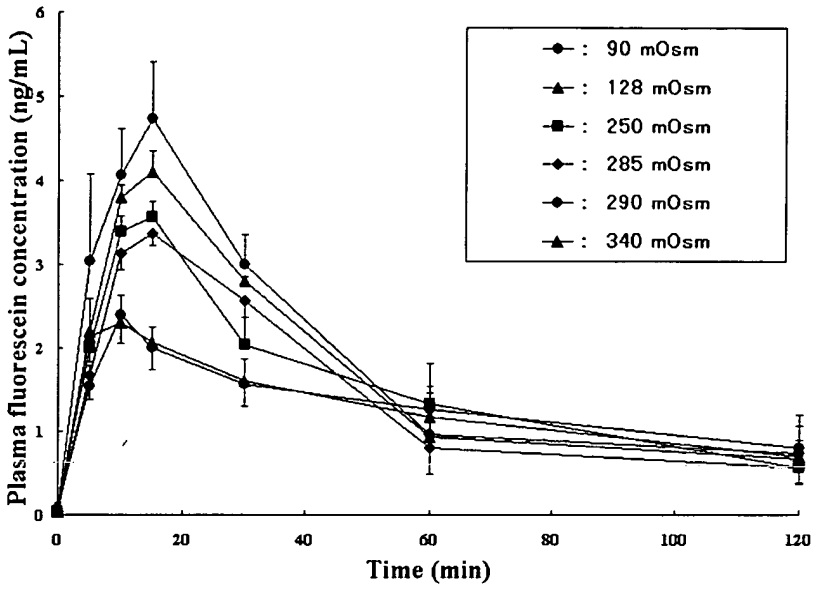
Therefore, the effectiveness of this invention was evaluated by the plasma concentration of the fluorescein that is a model drug.

Table 1

		Plasma fluorescein concentration (ng/mL)						
		0 min	5 min	10 min	15 min	30 min	60 min	120 min
Composition A 290 mOsm	Rabbit 1	0.1	1.6	2.5	2.0	1.5	1.3	0.5
	Rabbit 2	0.0	2.0	2.8	2.5	2.2	1.8	1.4
	Rabbit 3	0.1	1.0	1.9	1.5	1.0	0.7	0.5
	Average	0.1	1.5	2.4	2.0	1.6	1.3	0.8
Composition 12 340 mOsm	Rabbit 1	0.0	1.5	1.8	1.5	1.0	0.4	0.2
	Rabbit 2	0.0	2.2	2.3	1.9	1.6	1.2	0.5
	Rabbit 3	0.2	2.7	2.8	2.8	2.2	1.9	1.4
	Average	0.1	2.1	2.3	2.1	1.6	1.2	0.7
	t-test	NS	NS	NS	NS	NS	NS	NS
Composition B 285 mOsm	Rabbit 1	0.0	1.5	2.7	3.2	2.5	0.6	0.5
	Rabbit 2	0.1	2.3	3.5	3.7	2.2	0.3	0.2
	Rabbit 3	0.0	1.2	3.2	3.2	3.0	1.5	1.0
	Average	0.0	1.7	3.1	3.4	2.6	0.8	0.6
	t-test	NS	NS	NS	P<0.05	NS	NS	NS
Composition C 250 mOsm	Rabbit 1	0.1	1.9	3.0	3.3	1.0	0.5	0.0
	Rabbit 2	0.0	2.1	3.5	3.4	2.1	1.1	0.4
	Rabbit 3	0.0	2.0	3.7	4.0	3.0	2.4	1.3
	Average	0.0	2.0	3.4	3.6	2.0	1.3	0.6
	t-test	NS	NS	P<0.05	P<0.05	NS	NS	NS
Composition 7 128 mOsm	Rabbit 1	0.1	1.3	3.5	3.8	2.7	0.1	0.3
	Rabbit 2	0.0	2.5	3.8	3.8	2.9	1.0	0.7
	Rabbit 3	0.0	2.8	4.1	4.7	2.8	1.7	1.0
	Average	0.0	2.2	3.8	4.1	2.8	0.9	0.7
	t-test	NS	NS	P<0.05	P<0.01	NS	NS	NS
Composition D 90 mOsm	Rabbit 1	0.1	1.2	3.0	4.0	2.8	0.4	0.3
	Rabbit 2	0.2	2.6	4.0	3.9	2.4	0.4	0.1
	Rabbit 3	-0.1	5.3	5.2	6.3	3.8	2.1	1.8
	Average	0.1	3.0	4.1	4.7	3.0	1.0	0.7
	t-test	NS	NS	NS	P<0.05	NS	NS	NS

NS : No Significance

Graph 1



Plasma fluorescein concentration in 15 minutes after the administration (C_{15min}) were shown in Table 2 of each composite. Furthermore, C_{15min} between composition A (290mOsm) and compositions 7 and B-D (less than 290mOsm), and between composition A (290mOsm) and composition 12 (340mOsm), were statistically analyzed and shown in Table 2.

Table 2

	Composition A	Composition 12	Composition B	Composition C	Composition 7	Composition D
Osmolarity (mOsm)	290	340	285	250	128	90
C_{15min}(ng/mL)	2.0	2.1	3.4	3.6	4.1	4.7
t-test		NS	P <0.05	P < 0.05	P < 0.01	P < 0.05

NS : No Significance

3. Conclusion

The plasma fluorescein concentrations of composition A (290 mOsm) and composition 12 (340 mOsm) were almost the same and low level.

However, the plasma fluorescein concentrations of compositions of lower osmolarity than 290mOsm were higher than those of composition A (290 mOsm) and composition 12 (340 mOsm).
Then, the composition of lower osmolarity than 290 mOsm in this invention is effective for both systemic and topical drugs.

The plasma fluorescein concentrations of Compositions of lower osmolarity than 290mOsm were rapidly increased and reached to maximum concentration in 10 to 15 minutes after administration. The plasma fluorescein concentrations in 15 minutes after administration were 1.7 to 2.35 times higher than that of composition A (290 mOsm) and there were statistically significant difference.
The phenomenon that plasma fluorescein concentration goes up promptly after administration is showing this invention is extremely useful for the drug expected quick action like migraine remedy.

It was proven that the compositions in this invention are effective even in either case of the drugs for systemic action or topical action and extremely effective for the drugs that quick action was expected.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 17 day of July ,2002

永野 篤弘

Atsuhiro Nagano